IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Abraham J. Domb and Joseph S. Wolnerman

Serial No.: 10/083,413 Art Unit: 1655

Filed: February 27, 2002 Examiner: Flood, Michele C.

For: *ABSORBABLE SOLID COMPOSITIONS FOR TOPICAL TREATMENT OF ORAL MUCOSAL DISORDERS*

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO EXAMINER'S ANSWER

Sir:

This is a reply brief to the Examiner's Answer mailed March 14, 2007, in the above-referenced application. Submitted with this Reply Brief is a Request for Oral Hearing. The Commissioner is hereby authorized to charge $500, the fee for a Request for Oral Hearing for a small entity, to Deposit Account No. 50-3129.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(1) whether claims 1-4, 6, 15-17, 22-24, and 38 are novel as required by 35 U.S.C. § 102(b) over U.S. Patent No. 4,772,470 to Inoue *et al.* ("Inoue").

(2) whether claims 1-3, 15-17, 22-24, 26, and 38 are novel as required by 35 U.S.C. § 102(b) over U.S. Patent No. 4,226,848 to Nagai *et al.* ("Nagai").

(3) whether claims 1-4, 6-12, 15-17, 19, 22-24, and 38 under 35 U.S.C. 103(a) over Inoue in view of U.S. Patent No. 5,939,050 to Iyer ("Iyer") and U.S. Patent No. 6,197,305 to Friedman *et al.* ("Friedman").

(7) ARGUMENT

Appellants affirm all of the arguments made in the Appeal Brief.

(1) Rejections Under 35 U.S.C. § 102

Claims 1-4, 6, 15-17, 22-24, and 38 were rejected as being unpatentable under 35 U.S.C. § 102(b) over U.S. Patent No. 4,772,470 to Inoue *et al.* ("Inoue"). Claims 1-3, 15-17, 22-24, 26, and 38 were rejected as being unpatentable under 35 U.S.C. § 102(b) over U.S. Patent No. 4,226,848 to Nagai *et al.* ("Nagai").

Analysis

a. U.S. Patent N o. 4,772,470 to Inoue et al. ("Inoue")

Claim 1, 4, 6, 15-17, and 23-24 are not anticipated by U.S. Patent No. 4,772,470 to Inoue *et al.* ("Inoue")

Inoue describes an oral bandage comprising a soft adhesive film comprising a mixture of a polycarboxylic acid and/or a polycarboxylic acid anhydride and a vinyl acetate polymer and having incorporated therein a topical drug (abstract). The oral bandage may solely contain the adhesive film or may further contain a soft film support in combination with the adhesive film (col. 8, lines 30-33).

In the Examiner's answer, the Examiner states that "since Inoue clearly teaches incorporating topical drugs into the prior art composition in an amount from 0.0001 to 35% by weight based on the oral preparation, the remaining weight portion of the prior art composition comprising the bioadhesive carrier is deemed to be in an amount encompassed by about 40 to 99% based on the weight of the composition "(*see* page 13, lines 3-9). The Examiner provides no evidence to support this statement.

Indeed, this statement is contradicted by the disclosure in the patent. Inoue discloses that in addition to the active agent, the composition can contain a basic substance to neutralize the polycarboxylic acid (col. 6, lines 41-60). The film can also contain other additives, such as colorants, flavorants, and/or softening agents (col. 10, lines 5-14), as well as residual solvent from the casting process.

Further, the Examiner fails to address the applicants' arguments presented in the appeal brief regarding the fact that the examples describe laminating the polycarboxylic acid-polyvinyl acetate film to a support. No information is given regarding the weight of the support film, thus the weight percent of the bioadhesive material cannot be determined. Inoue does not disclose or

suggest a solid, self-bioadhesive composition comprising a pharmaceutically acceptable carrier comprising a mucoadhesive synthetic polycarboxylic acid polymer in an amount from about 40 to 99 percent based on the weight of the whole composition. Accordingly, claims 1, 4, 6, 15-17, and 23-24 are novel over Inoue.

Claim 2, 3, and 38 are not anticipated by Inoue

The compositions described in Inoue are films. Inoue does not disclose or suggest disks having the diameters and thicknesses specified in claims 2 and 3. Further, Inoue does not disclose or suggest a composition wherein the surface area is from about 0.4 to 3 cm^2 as defined in claim 38. The Examiner alleges that the films described in Inoue have a thickness of at least 5 μm, which encompasses larger thickness, such as 400 μm. Inoue discloses that the thickness of the polycarboxylic acid-polyvinyl acetate films is preferably in a range from 5 to 100 μm, which is equivalent to 0.005 to 1 mm (1 μm = .001 mm). This is not within the range of 0.4 to 2.3 mm in claim 2 or 1 to 2 mm in claim 3. Inoue goes on to state that "a film having a thickness exceeding 100 μm tends to produce a feeling foreign to the mouth and to impair softness of the film (col. 8, lines 15-17).

The Examiner alleges that Inoue discloses films having a width from 7 to 15 mm and diameter ranging from 5 mm to 20 mm and cites col. 8, lines 45-61 as support for this allegation. Col. 8, lines 45-61 discloses the thickness of the supporting film and the thickness of the composite film (thickness of the adhesive film plus thickness of the support film). The thickness of the support film is from 10 to 100 μm (0.01 to 1 mm) (col. 8, lines 53-55). The thickness of

the composite film is from 30 to 150 μm (0.03 to 0.15 mm). These thicknesses are not within the ranges specified in claims 2 and 3. Accordingly, claims 2, 3, and 38 are novel over Inoue.

Claims 22 and 26 are not anticipated by Inoue

Claim 22 depends from claim 1 and specifies that the solid bioadhesive carrier is a crosslinked synthetic polycarboxylic acid polymer. Claim 26 depends from claim 22 and specifies that the solid bioadhesive carrier is a polyacrylic acid polymer crosslinked with a polyalkenyl polyether, carboxymethylcellulose, hydroxymethylcellulose, or mixtures thereof. Inoue does not disclose or suggest a composition wherein the solid bioadhesive carrier is one or more crosslinked synthetic polycarboxylic acid polymers. The compositions described in Inoue contain a mixture of a polycarboxylic acid and/or a polycarboxylic acid anhydride and a vinyl acetate polymer. There is no disclosure in Inoue that the polymers are crosslinked.

The Examiner alleges that neutralizing polymers using polyvalent metal salts, such as oxides of zinc, calcium, magnesium, and the like inherently causes crosslinking of the polymer. The Examiner points to the disclosure of Odian (Principles of Polymerization) as support for her argument. A review of the passage marked by the Examiner shows that Odian discloses that neutralization of ethylene copolymers containing 5-10% acrylic or methacrylic acid copolymer with a metal salt yields products referred to as ionomers. Ionomers, according to Odian, act like reversibly crosslinked thermoplastics as a result of *microphase separation* between ionic metal carboxylate and non-polar hydrocarbon segments. The Examiner has misinterpreted Odian. Odian does not disclose that ionomers are cross linked materials; Odian discloses that ionomers

act like crosslinked polymers due to microphase separation. Even if one could argue that ionomers are crosslinked polymers, there is no disclosure in Inoue or Odian that such a phenomenon occurs in a mixture of polycarboxylic acid polymers and vinyl acetate polymers, which are required in Inoue. Finally, Inoue does not disclose or suggest crosslinked polycarboxylic acid polymers in combination with a polymer selected from the group consisting of polyalkenyl polyether, carboxymethylcellulose, hydroxymethyl cellulose, and mixtures thereof as specified in claim 26. Accordingly, claims 22 and 26 are novel over Inoue.

b. U.S. Patent No. 4,226,848 to Nagai

Claims 1-3, 22-24, 26, and 38 are not anticipated by Nagai

Nagai describes pharmaceutical preparations comprising a water-swellable and mucosa-adhesive polymeric matrix comprising about 50% to about 95% by weight of a cellulose ether and about 50 to about 5% by weight of a homo or copolymer of acrylic acid and dispersed therein a pharmaceutically effective amount of medicament (abstract). Nagai does not disclose or suggest a composition containing an herbal active agent wherein the agent is a bioactive herb, a tincture, an essential oil, or mixtures thereof. With respect to herbal extracts, the specification describes the preparation of herbal extracts on page 15, line 17 to page 17, line 2. Herbal extracts are prepared by the extraction of dry herbs. The resulting extracts typically contain several different compounds; the extracts are not a single compound derived from a natural source as described in Nagai. Furthermore, even though the compounds in Nagai cited by the

Examiner were originally isolated from natural sources, these compounds are typically prepared synthetically. Accordingly, claims 1-3, 23-24, 26, 27, and 38 are novel over Nagai.

Claims 15-17 are novel over Nagai

Claim 15 is dependent on claim 1 and specifies that the composition further comprises a non-herbal active agent. Claims 16-17 specify particular non-herbal active agents which can be used in the claimed composition in combination with one or more herbal active agents. As discussed above, Nagai does not disclose or suggest compositions containing bioactive herbs, herbal extracts, tinctures, essential oils, and/or mixtures thereof as required by claim 1. Accordingly, claims 15-17 are novel over Nagai.

(2) Rejections Under 35 U.S.C. § 103

Claims 1-4, 6-12, 15-17, 19, 22-24, and 38 were rejected as being unpatentable under 35 U.S.C. 103(a) over Inoue in view of U.S. Patent No. 5,939,050 to Iyer ("Iyer") and U.S. Patent No. 6,197,305 to Friedman *et al.* ("Friedman") with evidence provided by Lawless, The Illustrated Encyclopedia of Essential Oils ("Lawless").

Legal Standard

The standard for obviousness under 35 U.S.C. 103 was recently reaffirmed by the U.S. Supreme Court in KSR Int'l. Co. v. Teleflex, Inc, 2007 U.S. LEXIS 4745; 75 U.S.L.W. 4289.

According to the Supreme Court,

"often it will be necessary ... to look to interrelated teachings of multiple patents; the effects of demands known to design community or present in the marketplace; and the background

knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

In response to this decision, on May 3, 2007, the Assistant Commissioner of the U.S. Patent Office Margaret Facarino sent to the Technology Center Directors a memo, stating in relevant part:

(1). The court reaffirmed the *Graham* factors in the determination of obviousness under 35 U.S.C §103(a). The four factual inquiries under *Graham* are:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims at issue;

(c) resolving the level of one of ordinary skill in the art; and

(d) evaluating evidence of secondary consideration.

Graham v. John Deere, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966)

(2) The court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. §103(a).

(3) The court rejected the rigid application of the "teaching, suggestion or motivation" (TSM) test, which required a showing of some teaching, suggestion or motivation in the prior art

that would lead one of ordinary skill in the art to combine the prior art elements in the manner claimed in the application or patent before holding the claimed subject matter obvious.

(4) The court noted that the analysis supporting a rejection under 35 U.S.C §103(a) should be made explicit, and it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant art to combine the [prior art] elements" in the manner claimed.

"Therefore, in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed."

Analysis

Claims 1, 22-24, and 26 are not obvious over Inoue in view of Iyer and Friedman with evidence by Lawless

a. Inoue

As discussed above, Inoue does not disclose a composition comprising a bioadhesive carrier in an amount from about 40 to 99 percent based on the weight of the whole composition as required by claim 1.

b. U.S. Patent No. 5,939,050 to Iyer et al. ("Iyer")

Iyer describes antimicrobial compositions comprising at least two antimicrobial agents which exhibit reduced MIC values relative to the MIC values for the agents making up the combination when measured alone (abstract). Iyer does not disclose a solid, self-bioadhesive

formulation for topical application that adheres to the oral mucosal tissue. As noted at col. 7, lines 16-27 and lines 53-61, these formulations are oral rinses, mouth washes or cleansers.

c. U.S. Patent No. 6,197,305 to Friedman et al. ("Friedman")

Friedman describes an anti-fungal composition containing (a) an extract of botanical materials, the botanical materials including material from Echinacea species and Propolis; and (b) an essential oil (abstract). The composition can be in the form of a mouthwash, a suppository, or a cream. Friedman does not disclose a solid, self-bioadhesive composition for topical application that adheres to the oral mucosal tissue. The formulations are not bioadhesive. Ingredients such as those at col. 7 are either hydrophobic (such as beeswax) or liquid (glycerin and oil) or contain detergent (such as sodium lauryl sulfate). Table 3 describes a liquid mouthwash formulation, not a solid. Table 4 describes an oral gel primarily of polyethylene glycol, which is not bioadhesive alone. Tables 5 and 6 describe hydrophobic skin cream.

d. Lawless, The Illustrated Encyclopedia of Essential Oils ("Lawless")

Lawless describes that the essential oil of lemon contains approximately 70% limonene as well as sabinene, myrcene, and pinenes (page 120). Lawless does not disclose a self-bioadhesive composition for topical application that adheres to oral mucosal tissue, nor a homeopathic amount.

e. The references alone, or in combination, do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims (*In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974) "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art."). As discussed above, Inoue does not disclose a composition comprising a bioadhesive carrier in an amount from about 40 to 99 percent based on the weight of the whole composition as required by claim 1. The remaining references do not disclose or suggest the elements missing from Inoue. In order to establish a *prima facie* case of obviousness, the prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. One of ordinary skill in the art would not have been motivated to combine the non-bioadhesive, non-solid formulations of Iyer, Fiedman, and Lawless with the formulation of Inoue to arrive at the claimed compositions.

Accordingly claims 1 and 22-26 are not obvious over Inoue in view of Iyer and Friedman with evidence by Lawless.

Claims 2, 3, and 38 are not obvious over Inoue in view of Iyer and Friedman with evidence by Lawless

As discussed above, Inoue does not disclose the bioadhesive composition of claim 1 in the form of a disc having the diameters and thickness specified in claims 2 and 3. Inoue does not

disclose the composition of claim 1 having a surface area from about 0.4 to 3 cm^2. In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, neither Iyer, Friedman nor Lawless disclose or suggest solid compositions having the dimensions defined in claims 2, 3, and 38. Iyer, Friedman, and Lawless do not provide the elements missing from Inoue. Accordingly, claims 2, 3, and 38 are not obvious over Inoue in view of Iyer and Friedman with evidence by Lawless.

Claims 7-12 and 19 are not obvious over Inoue in view of Iyer and Friedman with evidence by Lawless

As discussed above, Inoue does not disclose or suggest the bioadhesive composition of claim 1. Inoue does not disclose or suggest a composition wherein the herbal active agent is an essential oil (claim 7-8), at least one monoterpene with three unsaturations (claim 9), or an essential oil which is a natural or synthetic mixture consisting of limonene and at least one myrcene, a-pinene, b-pinene, and sabinene characterized in that at least 60% by weight of the mixture is limonene (claim 10). Inoue does not disclose or suggest a composition comprising $MgBr_2$, NaCl, KCl, and mixtures thereof (claim 12) nor carnallite or a salt of carnallite (claim 13).

Iyer, Friedman, and Lawless do not provide the elements missing from Inoue. Iyer discloses antimicrobial compositions comprising at least two antimicrobial agents which exhibit reduced MIC values relative to the MIC values for the agents making up the combination when

measured alone. Friedman describes an anti-fungal composition containing (a) an extract of botanical materials, the botanical materials including material from Echinacea species and Propolis; and (b) an essential oil. Lawless describes that the essential oil of lemon contains approximately 70% limonene as well as sabinene, myrcene, and pinenes.

The Examiner alleges that Inoue discloses each and every element of the claims, except the herbal active agents recited in claims 7-15 and 19 and that the secondary references Iyer, Friedman, and Lawless discloses that the agents recited in claims 7-15 and 19 were useful in the making of topical compositions for the treatment of the oral mucosal tissue. The fact that the references disclose some of the compounds specified in claims 7-15 and 19 is immaterial. In order to establish a *prima facie* case of obviousness, the prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. One of ordinary skill in the art would not have been motivated to combine the non-bioadhesive, non-solid formulations of Iyer, Fiedman, and Lawless with the formulation of Inoue to arrive at the claimed compositions. Accordingly, claims 7-12 and 19 are not obvious over Inoue in view of Iyer, Friedman, and Lawless.

(8) SUMMARY AND CONCLUSION

Inoue does not disclose a bioadhesive composition comprising a pharmaceutically acceptable solid bioadhesive carrier, comprising a mucoadhesive synthetic polycarboxylic acid polymer, in an amount from about 40 to 99 percent based on the weight of the whole composition in a form suitable for administration and adhesion to the oral mucosa. Inoue does

Nagai does not disclose a solid, bioadhesive composition comprising at least one herbal active agent as defined in claim 1.

Iyer, Friedman, and/or Lawless do not disclose the elements missing from Inoue. Accordingly, the claims are not obvious over these references.

For the foregoing reasons, Appellant submits that claims 1-4, 6-12, 14-17, 19-26, and 38 are patentable.

Respectfully submitted,

/Patrea L. Pabst/
Patrea L. Pabst
Reg. No. 31,284

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PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2151
(404) 879-2160 (Facsimile)